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Adipose-Derived Stem Cell Therapy for Pain Reduction in Intervertebral Disc Degeneration: A Retrospective Clinical Evaluation

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Abstract
Intervertebral Disk Degeneration (IVDD) describes the normal process in which an intervertebral disc deteriorates ever since for years and decades of living. This may be due to intermediate aging or cumulative wear and tear on the discs. One of the primary spinal mechanics aids is the vertebral disc. Between vertebral bodies, there is a cushion that connects them and acts as a shock absorber during regular activities under the weight-bearing system of the spine. IVDD has contributed seriously to the major LBP cases worldwide. Still, until now, treatments are mostly pain-based, either surgical or non-surgical methods to manage pain, and no disease-oriented because of the lack of understanding about the basic cellular and molecular processes that facilitate degenerative changes in the disc. While attempts are made to reverse the degenerative changes, ADSCs came into the limelight as candidates since their immune modulatory effect and multipotentiality make them attractive for regenerative therapy and pain amelioration. This paper highlights the therapeutic properties of ADSCs and their potential role in therapeutic intervention of IVDD from new perspectives, together with preclinical and clinical evidence-based and future directions.

Keywords: adipose-derived stem cells, intervertebral disc degeneration, low back pain, regenerative medicine.

Introduction

Think of not being able to enjoy the beautiful moments in life because you suffer from continuous lower back pain which makes it impossible for you even to perform simple day-to- day activities. This is a sharp pain that millions of people have to deal with in their daily lives around the world. IVDD is a leading cause of low back pain and the most prevalent disabling condition globally (Wu *et al*., 2020). While a host of options are available including physiotherapy, medications as well as epidural spine injections to name but a few these provide only limited benefit in terms of pain efficacy due to its conventional approach geared at "pain management" rather than the direct treatment for underlying degenerative disc.

Within regenerative medicine, one ray of hope is utilizing Adipose-Derived Stem Cells (ADSCs) for treating IVDD. (Sakai *et al*., 2005). is the foundational study that dealt with ADSCs and IVDD. The use of ADSCs in therapy for intervertebral disc degeneration (IVDD) is a newly emerging area and has developed rapidly over the last two decades. These cells have special characteristics and play multiple roles such as immune response modulation, reducing inflammation, and differentiation potential into different types of cells (Soufi *et al*., 2023). Even more intriguing, they are harvested from the patient's body fat tissue; therefore, making them perfect candidates to treat an ailment like degenerative disc disease.

Here we describe how the journey from bench side to bedside of ADSCs could revolutionize IVDD through this review article. The first thing we need to know is what happens during the degeneration of an intervertebral disc, then it will be clearer how ADSCs can contribute in the treatment of degenerative discs. An intervertebral disc provides cushioning between the vertebrae. During the process of normal aging their elasticity and hydration diminish, causing pain and decreased mobility (Adams & Roughley, 2006). A

range of factors including lifestyle choices like smoking, mechanical stress due to heavy lifting, and genetics can contribute to intervertebral disc degeneration (Zielinska *et al*., 2021). Aging, nutritional disorders, and trauma as well were also associated factors in IVDD **(Fig 1).** As we age, the water content and flexibility of our intervertebral discs gradually depletes making them less capable of withstanding damage and deterioration normally (Adams & Roughley, 2006). The health of the intervertebral disc can also be influenced by poor nutrition as they depend on nutrients that are delivered through the blood supply, and when it starts lacking proper nutrition deficiencies have a great impact on causing degeneration (Urban & Roberts 2003). Trauma can expedite the degenerative process, through repetitive stress and physical injuries that harm the intervertebral discs (Vo *et al*., 2016).

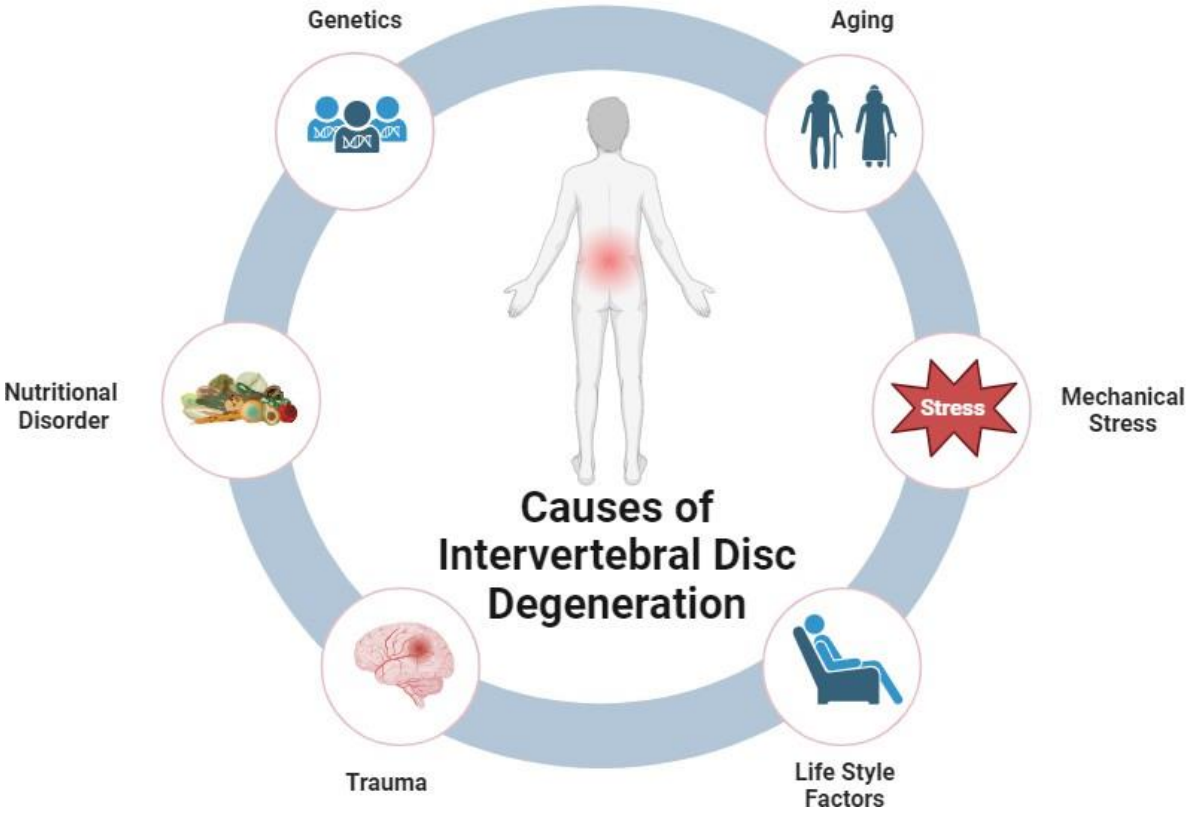

Fig 1: **Causes of IVDD:** The diagram illustrates the main factors contributing to IVDD including aging, mechanical stress, lifestyle factors, trauma, nutritional disorders, and genetic predisposition. IVDD, Intervertebral Disc Degeneration.

Intervertebral discs are sophisticated fibro-cartilaginous synovial joints that join the vertebral bodies. There is a central gelatinous nucleus pulposus, which is surrounded by the annulus fibrosus **(Fig 2).** Similarly, it is sandwiched between two cartilaginous endplates of an intervertebral disc. The intervertebral disc is comprised of annulus fibrosis which provides strength and containment, as well as the nucleus pulposus which absorbs compressive forces and therefore allows elasticity (Roberts *et al*., 2006).

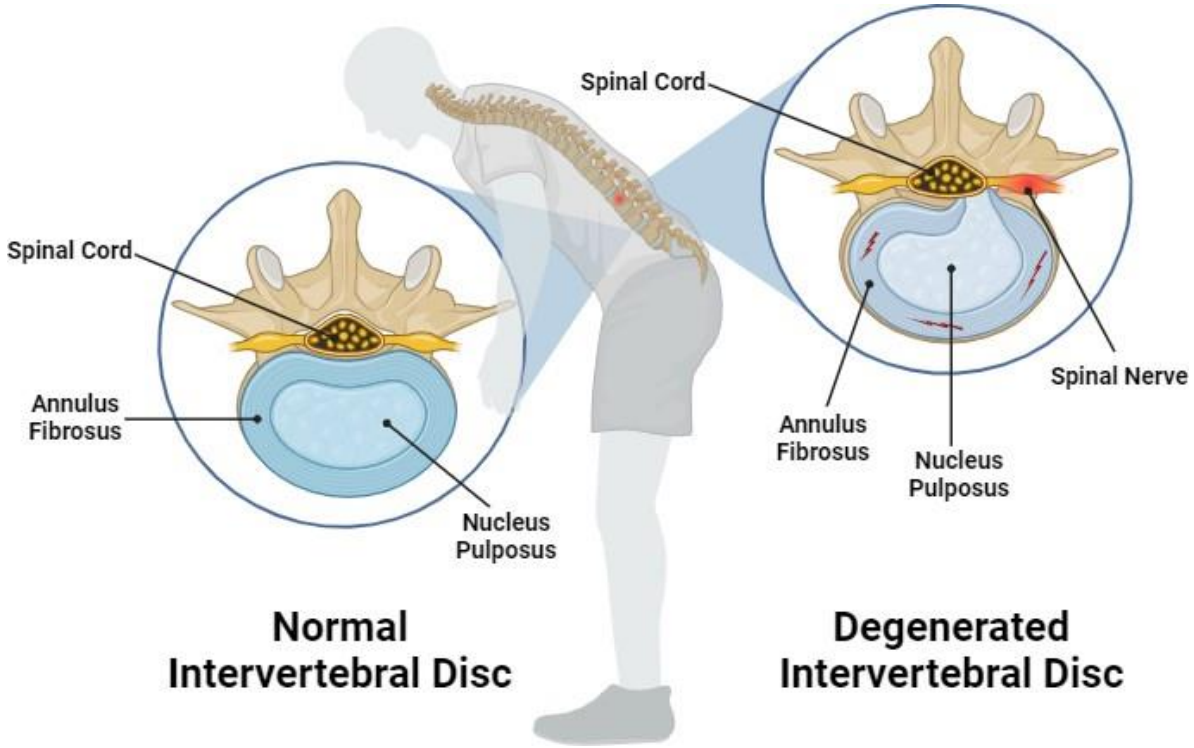

Fig 3: **Normal and degenerated intervertebral disc:** Annulus fibrosus, the outer layer of a normal disc that surrounds the nucleus pulposus to provide structural support but is torn or thin in a degenerate disc. Between the two vertebral bodies in each pair is an intervertebral disc, which consists of the nucleus pulposus - The center gel-like portion serves as a cushion and absorbs mechanical shock to protect our back anatomy, but the disc which has undergone degeneration shows loss of structural integrity and dehydration. A normal disc does not affect the spinal cord directly, while a degenerated disc may compress on the nerve which can cause pain.

Pathophysiology of IVDD

IVDD begins with the cascade of structural and biochemical changes. Hence, the first changes in a disc include the breakdown of its supportive framework — otherwise known as the extracellular matrix. This degradation leads to a decrease in proteoglycans and nucleus pulposus water content

The loss of water content in the nucleus pulpopsus results in dehydrated desiccation and loss of ability to maintain disc height/bear loads (Roughley, 2004; Vergroesen *et al*., 2015). At the same time, their hard outer layer i.e. annulus fibrosus is also cracked and very weak at this position which is another reason for instability (Freemont *et al*., 2002). Inflammatory molecules, like interleukin-1β and tumor necrosis factor-α, actually set a cycle that results in more matrix destruction (which damages the cells) by attracting immune cells to the disc and maintaining an environment that drives continued degeneration (Risbud & Shapiro 2014). Because of the inflamed state, this further causes damage leading to more chronic pain and disc injury. However, it is safe to say nerve endings within the disc become more pain- sensitive (Wuertz *et al*., 2012).

Adipose-Derived Stem Cells: A New Frontier

Mesenchymal stem cells have self-renewal ability and exist in different tissues or organs such as the adipose, bone marrow, lung liver cord blood, and fallopian tube (Mohammadian *et al*.,2013). Adipose-derived cells or ADSCs are the type of mesenchymal stem cells, harvested from body fat. They are harvested from the abdominal and thigh fat deposits using minimally invasive techniques (Gimble *et al*., 2007).

ADSCs are a special type of cell that can be used in regenerative medicine, making it attractive since they have the property to develop into various specific forms.

Differentiation Potential: ADSCs can differentiate into essential cell types for tissue repair. The key feature of ADSCs is their capacity to differentiate in chondrocytes, which are pivotal for the regeneration of

cartilaginous tissues in intervertebral discs (Liang *et al*., 2022). Applications to treat cartilage loss and degradation -- ADSCs have this ability, especially for disease conditions such as IVDD.

Immunomodulation: ADSCs have also been named as regenerative cells, which can regulate the immune system. ADSCs secrete growth factors and anti-inflammatory cytokines in situ microenvironment to modulate immune responses locally. It is also their exceptional ability to modulate immunity, participation in inflammation reduction as well an environment for wound healing inside damaged tissue (Stojanović & Najman, 2019). In addition, ADSCs themselves also have anti-inflammatory actions and can decrease the damage induced by chronic inflammation through their regulatory effect on an exaggerated immune response.

Paracrine Effects: Devoid of differentiation, ADSCs secrete bioactive molecules into the vicinity (pancreas signaling). The signaling molecules involved in wound healing are varied and include cytokines (such as interleukins), growth factors that regulate multiple target cells or processes relevant to damage control, and extracellular vesicles of many types mediating a wide range of effects. ADSCs contribute to tissue regeneration by enhancing angiogenesis, cell survival, and modulating the activity of surrounding cells (He *et al*., 2019). This paracrine activity emphasizes the ability of ADSCs to offer therapeutic roles other than just directly replacing cells.

Harvesting, Processing, and Transplanting Adipose-Derived Stem Cells

Harvesting Adipose Tissues

The first step is harvesting adipose tissue from the patient's body **(Fig 3).** Liposuction is generally the minimally intrusive way this procedure is performed. Liposuction is the removal of fat from certain parts, such as the abdomen thighs, or buttocks using a cannula. The harvest of adipose tissue is generally associated with minimal morbidity and it has been well tolerated by patients (Troell & Robert, 2014; Lamblet *et al*., 2022).

Processing Adipose Tissues

After harvesting adipose tissue, processing is required to isolate ADSCs. Several key steps are involved in processing:

Mechanical and Enzymatic Digestion:

The harvested fat is initially mechanically broken into small pieces. Enzymatic digestion using collagenase subsequently degrades the extracellular matrix, allowing the extraction of ADSCs from their respective tissue niche (Aronowitz *et al*., 2015). Whilst collagenase is used to ensure the efficient isolation of cells, there are limitations in terms of concentration and duration that must be tightly controlled if high cell viability levels

Centrifugation:

After initial enzymatic digestion, ADSCs are separated from blood cells and debris by centrifugation of the cell suspension. After centrifugation, a pellet is formed that contains the stromal vascular fraction (SVF) which harbors ADSCs (Aronowitz *et al*., 2015).

Cell Sorting and Expansion:

Subsequent processing of the SVF is performed to purify ADSCs by flow cytometry or magnetic bead sorting. Isolated ADSCs are expanded in culture using specialized media before transplantation to increase the number of cells (Khazaei *et al*. 2022). This implies a need to expand the cells before clinical application as obtaining sufficient cell numbers is critical.

Autologous Adipose-Derived Stem Cell Transplantation:

The expanded ADSCs are transplanted to the target site in the last phase **(Fig 3).** ADSCs are usually locally injected into degenerated discs (through a minimally invasive method).

Key factors for a successful introduction of ADCs include:

Injection Technique:

The disc is localized with a fine needle or cannula using the direct injection of ADSCs. The implantation of cells is undertaken through fluoroscopy or MRI imaging guidance to guarantee an accurate placement (Migliore *et al*. Therefore, the right technique is crucial for optimal cell delivery and to minimize complications.

Post-Transplantation Care:
Following transplantation, the patient may need transplant post-operative care to improve results from treatment. Such treatment will involve pain management, physical therapy, and regular follow-ups to track the integration and effects that have come about due to transplanted cells. In addition, the care of pain management seeks patient comfort and physical therapy is important in maintaining mobility and function (Mazini *et al*., 2021).
Long-term follow-up is necessary to evaluate the effectiveness and safety of ADSC therapy. This includes analyzing the clinical outcome, including pain relief and functional recovery as well as assessing monetization for possible side effects (Yuan *et al*., 2024).

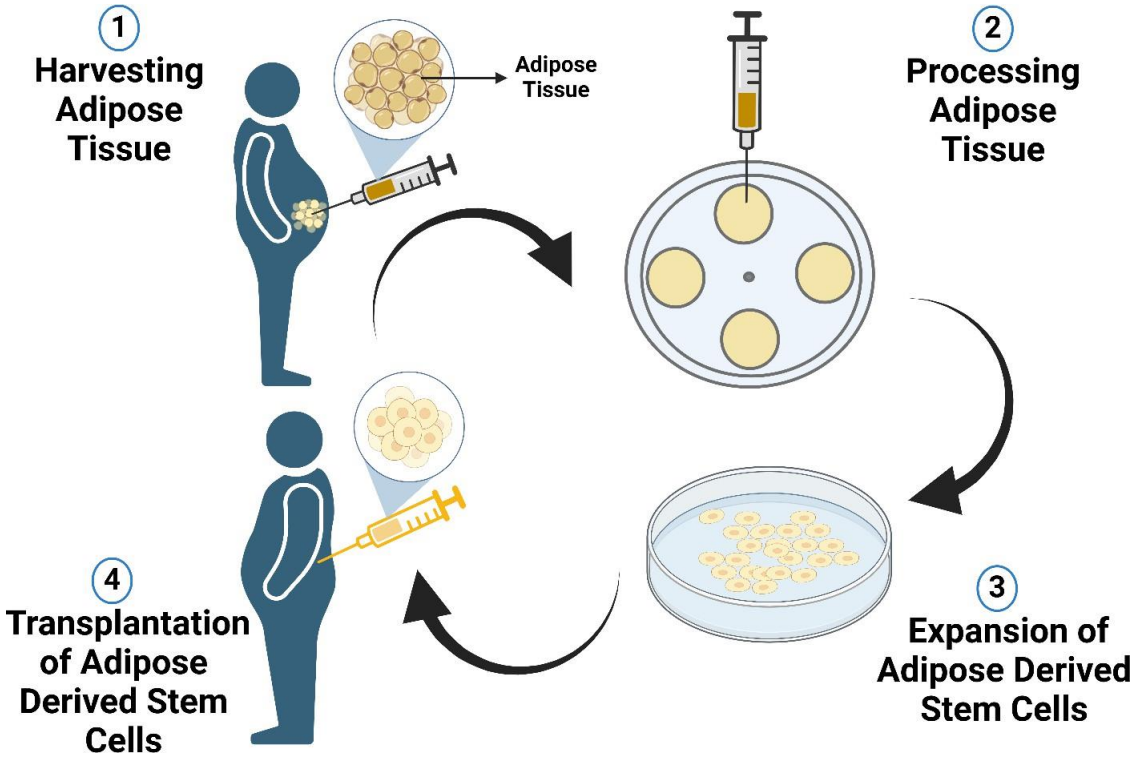

Fig 3: Workflow of ADSCs harvesting, processing, and transplantation workflow: Step 1 Harvesting adipose tissue from the patient's body. Step 2 The processing of adipose tissue to isolate ADSCs. Step 3 Expansion of ADSCs in specialized media. Step 4 The transplantation of expanded ADSCs into the target tissue.

Mechanism of Action
ADSCs can play their therapeutic role by different mechanisms. Once implanted in the body, these cells can redistribute themselves to the site of injury and differentiate into healthy disc cells that regenerate damaged discs by replacing dead or diseased tissue. Additionally, to promote tissue repairing and lessen the inflammatory response as well control ambient condition, ADSCs release abundance bioactive elements (Jia *et al*.2023).

Cellular Transformation: The Repair Crew
The normal structure and function of the disc is maintained by Nucleus pulposus, and ADSCs have Subsequently been reported to differentiate into nucleus pulposus-like cells (Sakai & Schol 2017). Under suitable culture conditions, ADSC demonstrated the ability to express genes of typical cells such as nucleus

pulposus cells (Sun *et al*., 2015). Upon integration, they can effectively act like the body's own repair crew by restoring integrity and function to the disc.

Bioactive Signaling: The Communication Hub

Indeed, ADSCs retain the property to release various bioactive molecules even when they are undifferentiated. In response to these signaling molecules, resident cells proliferate, improve tissue healing, and produce extracellular matrix components (Jia *et al*., 2023). This paracrine activity creates a supportive environment that inhibits cell death and stimulates regeneration rendering ADSCs a powerful healing tool.

Immune Modulation: The Peacekeepers

Modulation of immune response is only one of the unique features of ADSCs. In the inflamed microenvironment of a degenerative disc, they mediate environmental peacekeeping by inhibiting pro-inflammatory cells and promoting the availability of anti-inflammatory cells (Molinos *et al*., 2015). As a consequence, this transition to an anti-inflammatory environment effectively decreases pain and turns their environment into an ideal regeneration state.

Tissue Integration: The Architects of Repair

ADSC functions cannot be limited to secreting paracrine factors since this stromal subpopulation may contribute directly to potentially damaged annulus fibrosis or nucleus pilposus. They help in the re-building of the extracellular matrix and then become a part of that structure, providing scaffolding for new tissue formation (Sheykhhasan *et al*., 2019:). This architectural role is essential for the restoration of an intact disc function and biomechanical properties.

Enhancing Vascularization: The Lifeline Providers

ADSCs promote angiogenesis i.e. growth of new blood vessels in the degenerated disc. Releasing the new tissue is starved, and dismantling without more efficient blood vessels to carry fresh nutrients by utilizing oxygen that would be supplied (He *et al*., 2019). This lifeline keeps the discs stable and healthy in the long term.

Preclinical Studies: Building the Foundation

Laboratory studies have produced promising results using ADSCs in disc degeneration models. Conversely, in animal studies, ADSC transplantation can retard disc degeneration or promote hydration and lead to regaining the disc height (Munda *et al*.,2024). For example, a study wherein rats treated with ADSCs demonstrated significant degenerated disc regeneration compared to an untreated control (Jeong *et al*. 2010). Here are a few other research studies that have touched on ADSCs' potential for disc regeneration. In a rabbit model of IVDD, the injection of ADSCs has also shown important improvement in degenerative disc content (Mern *et al*., 2021). They offer good quality evidence from preclinical studies that prompt clinical trials using ADSC therapy.

The regenerative potential of ADSCs has been thoroughly investigated in animal models. Sakai and colleagues performed transplantation of ADSCs to a rabbit model with IVDD, resulting in recovery of disc height accompanied by marked histological restoration making it an effective study for regeneration (Sakai *et al*.,2017).

Preclinical studies have revealed fairly detailed step-by-step mechanisms of ADSC-induced disc regeneration. It has been shown that ADSCs secrete various growth factors including transforming growth factor-β (TGF-β) and insulin-like growth factor 1(IGF-I), which drive matrix production as well as cell proliferation. It is essential to improve how regenerative ADSCs regenerate and repair discs (Dong *et al*, 2023)

It is necessary to ensure safety and effectiveness before applying ADSCs therapy in clinical practice. Several preclinical studies have demonstrated the safety and lack of side effects with ADSC transplantation (Skrypnyk *et al*., 2024). These results provide evidence that ADSC transplantation is a safe and effective therapeutic option for treating IVDD.

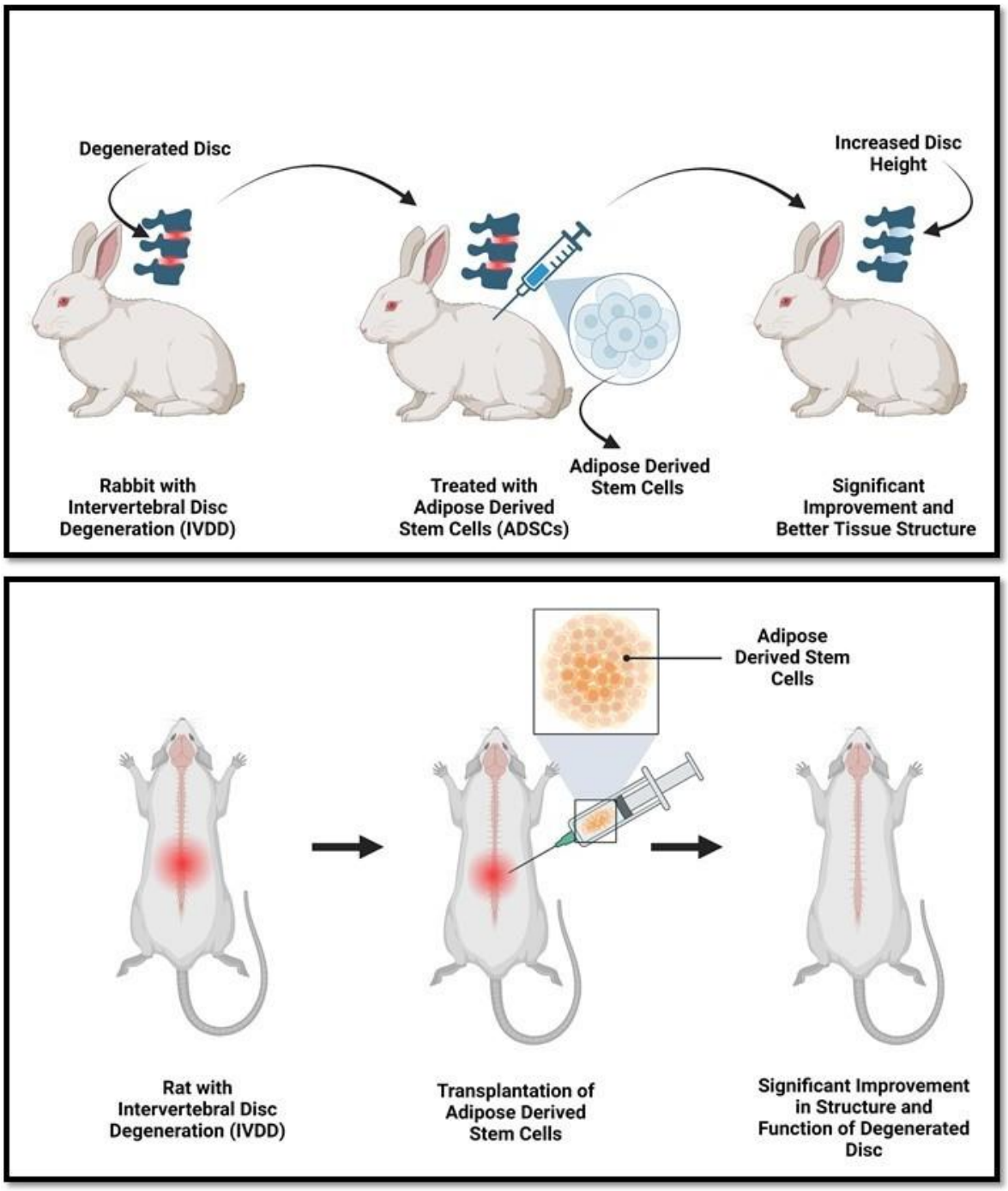

Fig 4: Therapeutic Effects of Adipose-Derived Stem Cells (ADSCs) on Intervertebral Disc Degeneration (IVDD) in Rabbit and Rat Models: This figure demonstrates the efficacy of ADSC therapy in preclinical models of IVDD. Both rabbit and rat models exhibit significant disc regeneration post-ADSC transplantation, underscoring the therapeutic potential of ADSCs in treating intervertebral disc degeneration

Clinical Evidence: Translating to Human Therapy

Compromise: The last mile between animal data and the clinic Currently, ADSC therapy has entered the early-phase clinical trial and appears to be a promising strategy for the treatment of IVDD by alleviating low back pain. An example is a study done by Fodor *et al*. (2016), ASDSC injections were associated with a significant reduction in pain and improvement in function at six months. These results are promising, but more extensive and long-term studies need to be carried out to confirm these benefits.

Numerous clinical trials have investigated whether the therapy can cure IVDD using ADSCs. This particular form of mesenchymal stem cell can be easily harvested from fat tissue with minimal effects on the donor site. These cells have the capacity to differentiate into a number of different cell types, including

chondrocytes, necessary for regeneration processes in intervertebral discs (Romaniyanto *et al*., 2022; Zhao and colleagues 2024).

In a study by Orozco *et al*. (2011), autologous ADSCs were obtained from subcutaneous adipose tissue, and a total of 6–12 × 10^6 cells/disc were injected directly into intervertebral disc of patients with low back pain due to DDD. The visual analogue scale (VAS) and Oswestry Disability Index(ODI) scores were reduced by 68% and 62.4% respectively in the study at the six-month follow-up. These improvements were maintained at 12 months with no deterioration in disc height. The water content on MRI scans was higher. Another interesting point is that 60% of the treated patient's injections were at a specific level L5-S1 disc, but its successful experiences did not rely on this site (Soufi *et al*., 2023)

In a prospective non-randomized study, autologous mesenchymal stem cells were injected into the intervertebral disc of 26 patients with low back pain (dose range: 1.72 to 4.5 million being an average dose per disc around 2.3 million). After 12 months, 88.5% of the participants experienced a 50% decrease in their VAS score, and 80.8% had at least a 40% reduction in their ODI scores. Autologous mesenchymal stem cell therapy for chronic low back pain secondary to degenerative disc disease: A conclusion was made that autologous mesenchymal stem cell infusion into the intervertebral space as a treatment of severe symptomatic DDD is safe and potentially effective (Soufi *et al*. 2023)

According to a report by Kumar *et al*. (2017), the feasibility, safety, and tolerability of combination implantation of ADSCs and an HA derivative was examined. Polysaccharides like hyaluronic acid derivatives are known to play a major role in the stabilization of extracellular matrix, hydration and increase viscoelastic properties (Sclafani *et al*. 2000). In this clinical trial, the results show that ADSCs combined with hyaluronic acid (HA) derivative provide a secure and effective option for IVDD treatment without serious adverse events, which may be an alternative to invasive surgery in patients.

In a clinical trial, both stromal vascular fraction (SVF) from adipose tissue via lipoaspirate and platelet-rich plasma by peripheral blood were used in combination to be conditioned for disc degeneration treatment. This study involves 15 people, who were able to flex their spines better and also had a considerable decrease in pain with less discomfort seen during the follow-up at six months, underlining that the therapy could be beneficial (Comella *et al*.,2017).

These excellent properties of ADSCs in regenerating intervertebral discs have been studied by several in vitro and in vivo experiments other than these clinical trials Adipose-derived stem cells (ADSCs) have been found to differentiate into nucleus pulposus-like cells under certain conditions such as hypoxia (Zhao *et al*., 2024), and within three-dimensional scaffolds. Nevertheless, many limitations and challenges remain for application in clinics to treat IVDD with ADSCs. Similarly, median effective doses of cell delivery or the time window suitable for intervention are yet to be defined conclusively (Zhang *et al*., 2022).

Beyond clinical and scientific presentations, patient perspective is important. Chronic low back pain significantly affects quality of life, daily activities, mental health, and productivity at work. Development of patient-reported outcomes and quality of life is required to address overall well- being.

Challenges and Future Directions

Despite the promise and encouraging outcomes using ADSCs in IVDD treatment, several challenges need to be overcome before accessing them for clinical application on a more universal basis. Thus standardization of isolation, expansion, and delivery methods are essential for improving the consistency of therapeutic outcomes with ADSCs. It is more important to standardize how ADSC should be prepared and delivered. Incorporation of non-standardized methods for isolation and culture cell types and non-optimized approaches to recovery, purification, and expansion reduce reproducibility. However, on the clinical side of things, a standardized protocol is essential for reproducibility and reliability. This will include optimizing the adipose tissue source, methods for cell isolation, and streamlining parameters required for in vitro expansion both as multi-potent cells or differentiation. Research studies were used different cell harvesting, isolation and culture techniques which affected the amount of cells harvested, purity of these cells as well as their functionality. In an attempt to address this issue, the International Federation for Adipose Therapeutics and Science (IFATS) together with the International Society for Cellular Therapy (ISCT) released a consensus statement detailing key aspects to be considered when isolating ADSCs (Zhang *et al*., 2020). Compliance with these guidelines would likely improve the quality and reproducibility of ADSCs for therapeutic applications.

There is also the issue of defining a cell dose and injection method suitable for IVDD therapy. The number of cells per injection delivered in the reviewed studies varied widely from 1.72 × 10^6 to 51.6 ×10^6, and it is unknown if higher cell doses result in better outcomes Additionally, the injection method (fluoroscopic guidance or discography), may affect distribution and retention of cells within the disc. More research is needed to establish the optimal cell dose and injection route for the treatment of IVDD.

Additionally, the long-term safety profile and potential risks of responses such as unwanted tissue growth or immuno-responses must be established. In addition to the basic research, long- term evaluation of safety and efficacy is also important for future clinical application of ADSC therapy. Studies had follow-up periods of 12 to 72 months. These studies demonstrated improvement in pain and disability scores, but there would still be a need for long-term experience to determine the longevity of the benefit along with any adverse events such as ectopic tissue formation or immune response. To address these limiting factors, investigation regarding standardization of ADSCs isolation and characterization as well as the optimal cell dose biologically active therapeutic amount within a given arguable limit for each application site with injection techniques must be established in future studies that should include more numerous randomized controlled trials which could have also longer duration follow up periods.

In addition, to improve the regenerative capacity of ADSCs and enhance therapeutic outcomes in combination with other strategies including supplementary growth factors or biomaterial scaffolds (Qin *et al*., 2023; Zhang *et al*., 2020). From a translational point of view, it is suggested that synergistic effects between ADSCs and other treatments should be explored to improve their therapeutic power. This would be useful for cell survival and integration, combining native microenvironment biomaterials that mimic the native disc environment (Yuan *et al*., 2024). Natural-synthetic combined, both natural and synthetic material scaffolds can provide structural support as well as hold the transplanted ADSCs in place.

An effective solution is to individualize treatments using the traits of each patient and disease stage. The therapeutic efficacy of ADSCs may improve the outcomes for patients with tailored strategies (Yuan *et al*., 2024). This may involve autologous ADSCs, tailored delivery methods and concurrent supplementary therapies optimized for the restorative processes that are involved.

As ADSCs are showing promise in the treatment of IVDD, researchers are looking for better ways to improve their therapeutic efficacy and extend its application. One attractive option is to combine the use of ADSCs with other modalities such as growth factors, biomaterial scaffolds, or gene therapy. One method that may improve the longevity and differentiation of ADSCs is genetic engineering, while ADSCs can be genetically stimulated to overexpress certain growth factors such as transforming growth factor-β (TGF-β) or bone morphogenetic protein-2 (BMP-2) which has been demonstrated to enhance disc regeneration effect (Trzyna & Banaś-Ząbczyk, 2021). On the other hand, ADSCs can also be incorporated into biomaterial scaffolds including hydrogels or fibrin matrices to establish a 3D supporting microenvironment that replicates native disc structure and promotes cell viability along with differentiation (Zhang *et al*., 2020).

A further interesting concept is the application of ADSCs from defined subpopulations or their modification to enhance regenerative capacities. ADSCs expressing CD271 and/or CD105 might further apply to disc regeneration, with higher chondrogenic potential (Zhang *et al*., 2020).

Ethical and Regulatory Considerations

Since ADSCs are obtained from adipose tissue, the ethical issues with stem cells such as embryonic can be sidestepped since no embryos have to be destroyed This feature significantly circumvents ethical objections associated with their use. Nevertheless, the ethics of informed consent remain problematic in providing patients with a full understanding of what it means to donate their adipose tissue for research and therapeutic purposes (Volarevic *et al*, 2018; West *et al*., 2014)

Ethical and Regulatory considerations are vital for utilizing ADSC for treating IVDD. As therapies develop, we need a code and standard to ensure ethical practices in both research and clinical delivery of stem cell-based interventions. From understanding basic ethical principles in stem cell research and therapy including informed consent, risk-benefit analysis, and protection of vulnerable populations to the legal framework governing regulatory aspects around the same. With any new therapy, ethical and regulatory concerns are on the top of mind. These samples need to be acquired ethically and with donor-informed consent. Regulatory agencies should also establish strict safety and efficacy guidelines for the clinical application of ADSCs.

Obtaining patient consent is necessary to perform clinical research and reflects a fundamental ethos of

conduct. Before people agree to take part in the study, they should be informed of all possible risks involved and how those risks may play a role. This is particularly important in stem cell research since the potential for unknown risks can still be higher. It is the responsibility of researchers to ensure that participants understand what information was given, and have a real choice in mooted questions. When working with a population with limited capacity to consent, this process is made even more difficult (e.g. children or individuals experiencing cognitive impairments). The process in these situations is such that it involves the need to request consent from a legal guardian so as not to go against what we consider ethical.

The risk-benefit ratio of the research is also an ethical consideration. Ethical guidelines dictate that the potential benefits of the study must outweigh the involved risks. It implies a full-fledged independent review by ethical committees/Institutional Review Board (IRB) for study design, methodologies, and anticipated results. These committees monitor ongoing studies and ensure the protection of human subjects during research among other responsibilities, as they take prompt action on adverse event reports (Kandi & Vadakedath, 2022) More specifically, in ADSC therapy of IVDD the long-term effects and potential complications related to stem cell injection should be thoroughly assessed for other pain-reducing function-enhancing results compared with risks involved by this procedure.

There is a complex landscape and how artificial dermis substitutes (ADSC) are approved for therapy under different countries' regulations. In the USA, stem cell products are regulated by the Food and Drug Administration (FDA) as biologics, requiring a biological product license which can be obtained upon demonstrating safety and efficacy with pre-clinical/clinical evidence before clinical use. The regulatory strategy aims to protect patients by requiring stringent scientific and technical criteria for stem cell applications. Nevertheless, the rapid strides in stem cell research combined with novel therapeutic utilities may occasionally precede contemporary regulatory adjuncts but those adjuvants should not be compromised mere lapse of vigilance over enforcement and regulation (Kandi & Vadakedath, 2022).

Regulatory bodies like FDA and EMA, play vital roles in every stage of development and clinical implementation for ADSC therapies. Therefore, clear guidelines and standards must be outlined to guarantee the safety of patients concerning isolation, characterization, and clinical application. This includes setting standards for cell quality, safety, and potency when designing clinical trials.

Conclusion

Stem cell therapy is a new and promising choice for the treatment of intervertebral disc degeneration (IVDD), among which adipose-derived stem cells(ADSCs) seem to be one. Hence, we assume ADSCs may have applications in treating IVDD. There is a great need for alternative treatments that target the cause of disc degeneration rather than providing symptom relief, including surgical procedures or pain medications. Given millions globally suffer from chronic low back pain, solutions are needed to address an underlying prevalent clinical problem. People are attractive targets for potential therapies, and ADSCs have properties that make them an effective treatment or mechanism of action.

ADSCs can differentiate into various types of cells, such as chondrocytes and nucleus pulposus- like cells that compose the intervertebral disc (Sakai & Schol, 2017). These properties are needed for repopulating a degenerated disc cell population, and restoring its structure integrity and function. Moreover, ADSCs secrete bioactive molecules that accelerate tissue regeneration, reduce inflammation and further enhance their therapeutic ability (Jia *et al*., 2023).

In addition, immunomodulatory properties represent an added therapeutic advantage of ADSCs against those clinical conditions. Through the modulation of local immune response, ADSC can establish a better environment projection for disc regeneration and attenuate chronic inflammation that is commonly observed in IVDD (Molinos *et al*., 2015). This anti- inflammatory capability is particularly relevant as degenerated discs are frequently in a pro- inflammatory state

The efficacy of ADSCs in animal models of disc degeneration has been partially addressed in preclinical studies. Studies showed the transplantation of ADSCs can restore disc height, improved hydration and histological structure in the disc (Munda *et al*.,2024). Human clinical trials have also come around and produced hopeful results, with patients experiencing sufficient pain relief as well as functional improvements post-treatment of ADSCs (Soufi *et al*., 2023).

The exciting results aside, there remain several hurdles to overcome before we can effectively use ADSCs in the treatment for sepsis and other inflammatory disorders; not least of which is establishing standardized

methods to isolate, expand, and deliver these stem cells. Addressing these challenges via rigorous research and clinical studies is necessary for achieving reliable therapeutic effects. Moreover, the synergistic effects of ADSCs with other treatments such as growth factors and biomaterials should also be considered to exploit the full regenerative potential of ADSC therapy (Yuan *et al*., 2024). Adoption of precision medicine strategies, where treatment regimens are customized for patient-specific characteristics or disease states on the horizon bodes well in optimization of therapeutic outcomes (Yuan *et al*., 2024). Moreover, the ethical and regulatory issues will be equally important in ensuring a sound clinical practice of ADSC therapy (Kandi & Vadakedath 2022).

In conclusion, ADSCs provide a new method for the therapy of IVDD. Because ADSCs target the source of disc degeneration and utilize their proliferative and regenerative potential comparable to cellular supplementation, we are likely viewing new horizons in IVDD. The hope is that further research, additional clinical trials, and long-term teamwork across disciplines will help us leverage the power of this novel therapeutic modality-a process that could ultimately result in an entirely new way to tackle chronic back pain down the line, as well be able to restore quality life for countless individuals.

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